Neurotherapeutics (2020) 17:1434–1455
https://doi.org/10.1007/s13311-020-00900-y

REVIEW

Complementary Therapies in Parkinson Disease: a Review of Acupuncture, Tai Chi, Qi Gong, Yoga, and Cannabis

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Published online: 12 August 2020

Abstract

Parkinson disease (PD) is a progressive neurodegenerative condition characterized by bradykinesia, rigidity, resting tremor, and postural instability. Non-motor symptoms, including pain, fatigue, insomnia, anxiety, and depression to name a few, are increasingly recognized and often just as disabling at motor symptoms. The mainstay of treatment is dopamine replacement; however, the beneficial effects tend to wane over time with disease progression, and patients often experience motor fluctuations and medication side effects. The lack of a disease-modifying intervention and the shortcomings of traditional symptomatic medications have led many patients to pursue complementary therapies to alleviate motor and non-motor symptoms associated with PD. The term complementary implies that the therapy is used along with conventional medicine and may include supplements, manipulative treatments (chiropractic, massage), exercise-based programs, and mind–body practices. As these practices become more widespread in Western medicine, there is a growing interest in evaluating their effects on a number of medical conditions, PD included. In this review, we provide an update on clinical trials that have evaluated the effectiveness of complementary treatments for patients with PD, specifically focusing on acupuncture, Tai Chi, Qi Gong, yoga, and cannabis.

Key Words Parkinson disease · complementary alternative medicine · acupuncture · Tai Chi · yoga · cannabis

Parkinson disease (PD) is a progressive neurodegenerative disorder affecting more than 1% of individuals over the age of 60, and the prevalence is expected to rise dramatically as the population ages [1]. PD is a clinical diagnosis that is based on the presence of cardinal motor features including bradykinesia, rigidity, resting tremor, and postural instability. These symptoms are often quite responsive to dopaminergic therapy early in the disease course, and levodopa remains the mainstay of symptomatic treatment. Despite a robust initial response to levodopa, patients tend to experience less consistent medication effects over time because of ongoing disease progression and increasing medication requirements, which can manifest as motor fluctuations (dyskinesia, wearing off, and sudden off periods) or medication side effects (hallucinations, orthostasis, and fatigue) [2]. Additionally, PD-related non-motor features (including cognitive, behavioral, sleep, and autonomic dysfunctions) are often progressive and may not respond to dopaminergic therapy, thus profoundly impacting quality of life [3, 4].

The lack of a disease-modifying treatment and the shortcomings of traditional symptomatic medications have led many patients with PD to pursue complementary therapies in addition to established, FDA-approved medications. According to the National Center for Complementary and Integrative Health (NCCIH), the term complementary refers to non-mainstream practices that are used *together with* conventional medicine, *versus* alternative, which indicates that the non-mainstream practice is used *in place of* conventional medicine [5]. Typically, these terms are used together as "complementary alternative medicine" or interchangeably. Complementary medicine encompasses a wide range of interventions, including supplements, manipulative therapies such as massage and chiropractic, physical exercise, and mind–body practices. Patients report using these therapies for motor and non-motor symptoms of PD, as well as for general health.

In survey-based studies prior to 2013, the use of complementary treatments to address any PD symptoms ranged from 26 to 76% in various countries around the world [6]. These

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numbers are expectedly higher in Asian populations, where many therapies that are viewed as complementary in Western medicine have been traditional practices for centuries. More recent surveys across the USA have reported increased use up to 50 to 74.1% [7–9] suggesting that interest in complementary treatments is growing.

In 2006, the American Academy of Neurology released an evidence-based review of disease-modifying and complementary therapies in PD [10]. At the time, they reported insufficient evidence to support or refute the use of acupuncture, manual therapy (i.e., chiropractic), or biofeedback. Since their report was published, the number of trials of various complementary therapies has vastly increased, as is demonstrated in this review. Despite growing interest in complementary therapies, there is generally a paucity of evidence that these practices are effective in treating the motor and non-motor symptoms of PD in randomized, controlled trials. Here, we review the available literature on several forms of complementary treatments as they have been studied in PD, including acupuncture, Tai Chi, Qi Gong, yoga, and cannabis.

Acupuncture

Acupuncture is a form of ancient Chinese medicine whereby thin needles are inserted into the skin at precise points (acupoints) in order to balance the flow of energy (*qi*) throughout the body. It is based on a theory that many different meridians run throughout the body and represent different organ systems, connected by these points [11]. Stimulating acupoints by needling, pressure, or heat can thus treat or cure specific ailments that are caused by dysfunction along the meridians [12]. While acupuncture has been a common treatment modality in Eastern medicine for thousands of years, it remains controversial due to mixed reports of efficacy. Still, it has taken hold as a complementary therapy in Western medicine for a wide variety of medical conditions, including many neurologic disorders [13–15]. Early open-label trials of acupuncture for patients with PD demonstrated safety and potential efficacy for motor [16] and non-motor [17, 18] symptoms, prompting further evaluation through randomized, controlled trials (Table 1).

Acupuncture for Motor Symptoms of Parkinson Disease

Because the diagnosis of PD is based on four cardinal motor features, many trials of acupuncture have used measures of motor dysfunction, including the Unified Parkinson's Disease Rating Scale, motor subscale (mUPDRS), to determine efficacy. In 2005, Cristian and colleagues [23] performed one of the first double-blind, sham-controlled, randomized studies of electroacupuncture (EA) in patients with PD, finding non-significant trends toward improvement on multiple motor and non-motor measures. Another randomized, controlled trial conducted in China using 10 sessions of acupuncture resulted in a significant decrease in the average levodopa dose relative to controls [21]. Cho and colleagues [24] compared regular acupuncture with bee venom acupuncture (BVA) and a third non-intervention control group and found that both acupuncture and BVA led to a significant improvement in mUPDRS score from baseline. In a subsequent trial by the same group, BVA was compared with sham acupuncture (twice weekly saline injections combined with acupuncture in sham acupoints) and conventional medical treatment [28]. After 12 weeks, both the acupuncture and sham groups showed significant improvement compared with controls on the mUPDRS. The BVA group improved from baseline in the mUPDRS, as well as the postural instability and gait disturbance (PIGD) score, Beck Depression Inventory (BDI), Parkinson's Disease Quality of Life Questionnaire (PDQL), and the number of steps to walk 20 m; however, this was not statistically significant compared to the sham acupuncture group [28]. Li and colleagues [30] randomized 41 patients with PD into acupuncture, sham, and waiting groups and found a significant improvement on the mUPDRS in the active treatment group, specifically the tremor scores. The acupuncture targeted acupoints DU20, GB20, and the chorea–tremor controlled zones, all of which are reported to alleviate tremor based on traditional Chinese theory.

Acupuncture for Gait and Balance in Parkinson Disease

In addition to targeting general motor disability related to PD, other trials have focused more on the specific issues of gait dysfunction and balance impairment. An open-label trial of acupuncture in 27 patients with PD demonstrated an immediate 10% improvement in gait speed, 8% improvement in step length, 11% increase in floor reaction force, and two additional steps per minute on testing of cadence [19]. In a small, sham-controlled trial, Toosizadeh and colleagues [25] found that weekly EA treatments over a 3-week period resulted in improved balance based on measurements of sway, and a significant improvement in mUPDRS (specifically rigidity scores) when compared to patients receiving the treatment at non-acupuncture points. The same group incorporated wearable sensors in 15 patients to demonstrate improvement in gait after three weekly electroacupuncture sessions, measured by gait speed (9–19% improvement on different measures), stride length (9% improvement), and mid-swing velocity (6% improvement) [26]. These results are encouraging but should be validated in longer duration, blinded trials.

Table 1 Reported clinical trials of acupuncture for patients with Parkinson disease

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Eng et al. (2006) [17]							
USA	25	Open-label	6 months	24 sessions of acupuncture with Tui Na massage and Qi Gong	–	Motor: 2.4 points worsening on mUPDRS from baseline Non-motor: 16% improvement on PDQ-39 ($p = 0.044$) and 29% improvement on BDI ($p = 0.006$) Qualitative: 3 reported no change, 4 mild, 9 moderate, and 7 marked improvement	Safe and well tolerated
Doo et al. (2015) [16]							
Korea	11	Open-label	12 weeks	24 acupuncture + BVA sessions	–	Motor: UPDRS parts II and III improved significantly from baseline (5-point improvement) Improved gait speed (2-s improvement) Non-motor: PDQL improved significantly from baseline (122 to 147)	Some reported slight bleeding or pain; some redness or itchiness with BVA. No serious adverse effects
Fukuda et al. (2015) [19]							
Japan	27	Open-label	1 visit	1 acupuncture session	–	Motor: improvement in gait speed (60.4 to 66.2 m/min, $p = < 0.001$), step length (53.7 to 57.7 cm, $p = < 0.001$), floor reaction force (0.26 to 0.29 m/s^2, $p = < 0.001$), and cadence (112.7 to 114.8 steps/min, $p = 0.007$)	Did not report
Shulman et al. (2002) [18]							
USA	20	Open-label	5 weeks or 8 weeks	Twice weekly acupuncture sessions	–	Motor: no improvement in mUPDRS or other quantitative motor assessments Non-motor: on SIP, only significant improvement in sleep and rest category ($p = 0.03$); no change in total score; no improvement in BDI or BAI Qualitative: 85% of patients reported subjective improvement of symptoms including tremor, walking, handwriting, slowness, pain, sleep, depression, and anxiety	Safe and well tolerated
Yu et al. (2019) [20]							
Taiwan	15	Controlled trial, groups assigned based on patient preference	8 weeks	Twice weekly acupuncture sessions ($n = 9$)	Usual care, with oral pain medications only ($n = 7$)	Motor: improvement in total UPDRS (− 21.6%, $p = 0.005$), but not motor subscale Non-motor: KPPS improved from baseline (− 46.2%, $p = 0.023$); no change in BDI, PDSS-2, and PDQ-39	
Ren (2008) [21]							
China	80	Randomized, controlled	Unspecified	2 courses of 10 sessions of acupuncture ($n = 50$) given every 3–5 days	Levodopa (Madopar) only ($n = 30$)	Motor: significantly lower dose of Madopar in the treatment group after intervention (752 mg *vs* 504 mg, $p < 0.05$)	Did not report
Aroxa et al. (2017) [22]							
Brazil	22	Randomized, controlled	8 weeks	Weekly acupuncture sessions ($n = 11$)	Usual care ($n = 11$)	Non-motor: PDSS showed significant improvement from baseline in sleep quality, nocturnal psychosis, and nocturnal motor symptoms compared to baseline; no difference between groups	Did not report

Table 1 (continued)

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Cristian et al. (2005) [23]							
USA	14	Randomized, controlled, double-blind	2 weeks	5 EA sessions ($n = 7$)	EA in non-acupuncture sites ($n = 7$)	Motor: non-significant trend toward improvement in mUPDRS Non-motor: non-significant trend toward improvement on PDQ-39 ADL subscale and summary index; no change in GDS Qualitative: subjective improvements in nausea and sleep	Did not report
Cho et al. (2012) [24]							
Korea	43	Randomized, controlled, double-blind	8 weeks	Twice weekly BVA ($n = 14$) or regular acupuncture sessions ($n = 15$)	Usual care ($n = 14$)	Motor: Both interventions had improvement in mUPDRS from baseline; BBS and 30-m walking time improved in BVA from baseline; total UPDRS and mUPDRS improved relative to controls in BVA Non-motor: BDI improved from baseline in the regular acupuncture group	One patient reported itchiness with BVA. No serious adverse events
Toosizadeh et al. (2015) [25]; Lei et al. (2016) [26]							
USA	15	Randomized, sham-controlled, double-blind	3 weeks	Weekly EA sessions ($n = 10$)	Sham acupuncture at placebo sites ($n = 5$)	Motor: Compared to baseline, the EA group had improved balance based on measures of sway and significant improvement in mUPDRS, specifically falls and rigidity (67% and 48%, respectively; $p = 0.02$); significant improvement in UPDRS II and III and rigidity subscale compared to controls ($p < 0.05$) In specific measures of gait and balance, significant improvement from baseline in speed, stride length, and mid-swing speed; improvement compared to controls in most measures of gait, especially speed (effect size 0.32–1.16, $p = 0.001$)	One patient with transient lightheadedness during procedure No serious adverse events
Kluger et al. (2016) [27]							
USA	94	Randomized, sham-controlled, double-blind	6 weeks	Twice weekly acupuncture sessions ($n = 47$)	Sham acupuncture with toothpicks at placebo sites ($n = 47$)	Motor: no improvement in mUPDRS in either group after 6 weeks Non-motor: no between-group differences on the MFIS, though both groups improved significantly from baseline at 6 weeks and 12 weeks	One patient reported constipation that resolved after stopping acupuncture
Cho et al. (2018) [28]							
Korea	73	Randomized, sham-controlled, double-blind	12 weeks	Twice weekly BVA sessions ($n = 29$)	Sham acupuncture with normal saline ($n = 29$), usual care ($n = 15$)	Motor: Compared to usual care, the BVA group had improvement in UPDRS II and III and PIGD, but not compared to sham acupuncture; both BVA and sham improved significantly from baseline on mUPDRS, 20-m step at 12 weeks, but only BVA had sustained improvements at 20 weeks Non-motor: PDQL improved in both groups at 12 weeks, sustained only in the BVA group at	Some patients reported mild pain or slight bleeding after acupuncture and mild itchiness or swelling after BVA No serious adverse events

Table 1 (continued)

Study	Size	Design	Intervention	Duration	Controls	Outcomes	AEs
						20 weeks, BDI was improved in the BVA group at 20 weeks	
Kong et al. (2018) [29]							
Singapore	40	Randomized, sham-controlled, double-blind	Twice weekly acupuncture sessions ($n = 20$)	5 weeks	Sham acupuncture with retractable needles ($n = 20$)	Motor: significant improvement from baseline on mUPDRS in the acupuncture group, but not compared to controls Non-motor: Both groups had significant improvement from baseline on the MFI, but no between-group differences; no improvement from baseline on PDQ-39, GDS, and ESS	2 serious adverse events from falls, not felt to be related to acupuncture; 1 worsening of anxiety

AEs = adverse events; BAI = Beck Anxiety Inventory; BBS = Berg Balance Scale; BDI = Beck Depression Inventory; BVA = Bee Venom Acupuncture; EA = electroacupuncture; ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; KPPS = King's Parkinson's Disease Pain Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; mUPDRS = Unified Parkinson's Disease Rating Scale, motor subscale; PDQ-39 = 39-item Parkinson's Disease Questionnaire; PDQL = Parkinson's Disease Quality of Life Questionnaire; PDSS = Parkinson's Disease Sleep Scale; PDSS-2 = Parkinson's Disease Sleep Scale 2; PIGD = Postural Instability and Gait Disturbance score; SIP = Sickness Impact Profile; UPDRS = Unified Parkinson's Disease Rating Scale

Acupuncture for Non-motor Symptoms of Parkinson Disease

In addition to monitoring motor function, many of these trials have also incorporated non-motor scales as secondary outcomes. Open-label trials report consistent improvement in quality of life [16, 17], depression [17], and sleep [18]. Activities of daily living (ADLs) improved in the experimental group of some controlled trials [23, 25], as did quality of life on the 39-item Parkinson Disease Questionnaire (PDQ-39) and depression on the BDI [24, 28].

Two randomized, controlled trials have evaluated the effects of acupuncture specifically on fatigue, as this is a common complaint among patients with PD. Kluger and colleagues [27] studied real *versus* sham acupuncture in 94 patients with PD reporting mild to moderate fatigue and found that there was no difference between the groups on the Modified Fatigue Impact Scale (MFIS) at 6 weeks and 12 weeks, though both had improved significantly from baseline. Similarly, a more recent study of 40 patients did not show a between-group difference in measures of fatigue, though both the acupuncture and sham groups had improvement in fatigue by week 5 that was sustained at week 9 [29].

Aroxa and colleagues [22] explored the use of acupuncture for sleep disorders in 22 patients with PD and found that there was a significant improvement in total Parkinson Disease Sleep Scale (PDSS), specifically in the domains of general sleep quality, nocturnal psychosis, and nocturnal motor symptoms compared to medication-only controls after eight weekly sessions.

Lastly, acupuncture has also been studied extensively for the treatment of pain conditions, and a recent study evaluated this specifically in PD. Sixteen patients scoring above zero on the King's Parkinson's Disease Pain Scale (KPPS) who had not had acupuncture within the prior 3 months self-selected into an acupuncture or non-intervention control group based on their personal preference. Patients who received acupuncture had significant improvement in the total UPDRS score and KPPS compared with controls, but no improvement in depressive symptoms [20].

Imaging and Acupuncture in Parkinson Disease

Researchers have used various imaging modalities to assess the effects of acupuncture on patients with PD, including single-photon emission computerized tomography (SPECT) imaging, functional magnetic resonance imaging (fMRI), and resting-state fMRI. In 2009, Huang and colleagues [31] published data on five patients with PD receiving levodopa and five patients with PD receiving levodopa plus acupuncture, showing increased glucose metabolism in the bilateral frontal and occipital lobes, and the temporal lobes, thalamus, and cerebellum on the less affected side. In a subsequent study, they found an increase in cerebral blood flow in the frontal lobe, occipital lobe, basal ganglia, and cerebellum in the more affected hemispheres of ten patients with PD who had received 5 weeks of EA, compared with ten patients on levodopa alone [32]. This did not show any change in basal ganglia dopamine transporter activity using 99mTc-TRODAT-1 SPECT imaging, suggesting that acupuncture has no effect on the pathophysiologic mechanisms underlying PD.

Chae and colleagues [33] studied ten patients with PD after receiving acupuncture, covert placebo, and overt placebo—all patients received the three procedures at different times, and fMRI was conducted after each. There was increased activity in the putamen and primary motor cortex after acupuncture compared with covert placebo, suggesting that this treatment may modulate the basal ganglia–thalamocortical circuit, thereby improving motor symptoms. Yeo and colleagues [34] performed a small, randomized, sham-controlled trial comparing twelve patients with PD to healthy controls specifically targeting the GB34 acupoint, which is thought to cure disease of the lower extremities (including pain and weakness), muscles, and gallbladder. Additionally, this region has demonstrated neuroprotection in MPTP mouse models [35–37]. Their results show a difference in activation between patients with PD and healthy controls at baseline and in their response to acupuncture, with increased activation of the precentral gyrus, prefrontal cortex, and putamen in those with PD. They subsequently performed an open-label evaluation of the effects of acupuncture at right GB34 and LR3 (an acupoint that can improve difficulty walking and lower extremity weakness, numbness, and pain), with additional acupoints based on individual symptoms. Changes in fMRI were noted in a variety of brain regions, but there was a statistically significant increase in thalamic response that was found to correlate with the change in mUPDRS [38]. In a 2018 trial, patients with PD received either real acupuncture, sham acupuncture, or standard medical therapy [30]. In addition to showing a 3.6 and 4.4-point improvement on the UPDRS II and III subscales, respectively, the fMRI showed modulation of the cerebello-thalamo-cortical circuit. This functional change corresponded to the significant improvement seen specifically on the mUPDRS tremor score. In the study by Yu et al. [20] that evaluated pain in patients with PD, post-acupuncture resting-state fMRI showed increased connectivity through four links: between the left middle temporal and precentral gyri, right postcentral and precentral gyri; right supramarginal and precentral gyri; and right medial temporal gyrus and insular cortex—all areas involved in sensory discrimination and emotion.

Conclusion

Studies of various forms of acupuncture in PD patients have provided mixed results regarding its effects on both motor and non-motor features. Open-label trials and those without sham control tend to favor the intervention. Larger, sham-controlled studies have been less effective at showing a meaningful improvement in the acupuncture group relative to controls, suggesting that the benefits may not be related to the intervention itself. In one such study, the authors concluded that the benefit observed in both groups could be related to non-specific effects, such as physical contact with acupuncturists, relaxation, and mind–body focus, or classic placebo effects [27]. Given that acupuncture is a relatively safe procedure, the reason that patients experience benefit may not be important, and it is reasonable to consider acupuncture as part of a multidisciplinary treatment approach for patients with PD.

Imaging studies provide supportive data of functional changes in response to acupuncture that may correlate to motor and non-motor improvements, but this needs to be evaluated in larger, long-term studies.

Tai Chi

Tai Chi, or *taiji quan*, is a traditional Chinese martial art practice that has been utilized for centuries to address physical and mental well-being. The term refers to the concept of yin and yang, which incorporates complex and disciplined movements to achieve dynamic balance, along with breathing and meditation. Tai Chi has been studied extensively for many medical conditions, including PD, and a review of Tai Chi for general health and fitness reports excellent evidence for improving balance and endurance [39]. Open-label trials of Tai Chi suggest that patients with PD may benefit with regard to obstacle negotiation [40] and awareness of movement [41]. A number of randomized, controlled trials have explored the effects of Tai Chi on motor and non-motor symptoms in further detail (Table 2).

Tai Chi for Motor Symptoms and Postural Instability of Parkinson Disease

Over the past two decades, the exploration of beneficial effects of Tai Chi on PD motor symptoms has provided mixed results. Many studies [43–47, 49, 50] have used non-exercise controls for comparison. Hackney and Earhart [43] reported improvement in the mUPDRS relative to those receiving usual care after 20 1-h-long Tai Chi sessions, while Choi and colleagues [47] found improvement after 36 sessions compared to baseline within the Tai Chi group, but not relative to controls. Two groups [45, 49] did not find significant improvements in the mUPDRS when compared to baseline, but one study did note improvement in balance on the Berg Balance Scale (BBS) [49]. Similarly, Vergara-Diaz and colleagues [50] compared those receiving a biweekly Tai Chi intervention with non-exercise controls, and while they did not find a

Table 2 Reported clinical trials of Tai Chi for patients with Parkinson disease

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Venglar (2005) [41]							
USA	1	Open-label	8 weeks	Weekly hour-long Tai Chi class	–	Motor: improvement in TUG test—both speed and number of steps Qualitative: increased awareness of how patient was moving, worsening of balance confidence on ABC scale	Did not report
Li et al. (2007) [42]							
USA	17	Open-label	5 days	Daily 90-min Tai Chi exercise program	–	Qualitative: The program was well received by all participants with respect to program appropriateness, participant satisfaction and enjoyment, and intentions to continue	The program was safe. No serious adverse events
Kim et al. (2014) [40]							
Korea	12	Open-label	12 weeks	3 Yang-style Tai Chi sessions per week	–	Motor: statistically significant improvement in anteroposterior (124%) and mediolateral (135%) displacement of the center of pressure compared to baseline	Did not report
Hackney and Earhart (2008) [43]							
USA	33	Randomized, controlled	10–13 weeks	20 60-min Yang-style Tai Chi training sessions ($n = 17$)	Non-exercise control group ($n = 16$)	Motor: significant improvement on BBS in the Tai Chi group relative to controls; non-significant trends toward improvement on mUPDRS, 6MWT, TUG test, tandem stance, and backward walking compared to controls Qualitative: All Tai Chi participants reported that they enjoyed the program and generally noted improvement in subjective measures of motor function	Did not report
Hackney and Earhart (2009) [44]							
USA	61	Randomized, controlled	20 weeks	40 sessions of Tai Chi ($n = 13$), tango ($n = 14$), waltz/foxtrot ($n = 17$)	Non-exercise control group ($n = 17$)	Non-motor: The tango group had significant improvement in PDQ-39 summary index, social support, and mobility subscales	Did not report
Amano et al. (2013) [45]							
USA	45	Randomized, controlled	16 weeks	2 or 3 60-min Yang-style Tai Chi sessions per week ($n = 27$)	Qi Gong meditation ($n = 9$) or usual care ($n = 9$)	Motor: ineffective in improving gait initiation, gait performance, or mUPDRS compared to controls	Did not report
Nocera et al. (2013) [46]							
USA	21	Randomized, controlled	16 weeks	3 60-min Yang-style Tai Chi sessions per week ($n = 15$)	Non-exercise control group ($n = 6$)	Non-motor: significant improvement on PDQ-39 total score (effect size = 1.03, $p = 0.04$) and emotional well-being subscale (effect size = 0.46, $p = 0.04$)	Did not report
Choi et al. (2013) [47]; Choi (2016) [48]							
Korea	20	Randomized, controlled	12 weeks	3 60-min Tai Chi sessions per week ($n = 11$)	Non-exercise control group ($n = 9$)	Motor: significant improvement from baseline on the mUPDRS in the Tai Chi group, and interaction effects (time *vs* group) on reaction time and one leg balance; a secondary analysis of functional fitness showed significant	Did not report

Table 2 (continued)

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
						improvement in arm curls, functional reach, and one leg balance compared to baseline. Non-motor: significant improvement from baseline on UPDRS mentation, behavior, and mood subscale	
Gao et al. (2014) [49]							
China	76	Randomized, controlled	12 weeks	3 60-min Yang-style Tai Chi sessions per week ($n = 37$)	Non-exercise control group ($n = 39$)	Motor: significant improvement on the BBS compared to controls, though no improvement in mUPDRS or TUG test; the Tai Chi group had fewer falls than controls	Did not report
Vergara-Diaz et al. (2018) [50]							
USA	32	Randomized, wait-list-controlled	6 months	Average of 2 Tai Chi sessions per week ($n = 16$)	Non-exercise control group ($n = 16$)	Motor: non-significant trend toward improvement in ABC and TUG test Non-motor: non-significant trend toward improvement in PDQ-39; both groups improved on trail-making test, though not significant	No adverse events related to the intervention
Li et al. (2012) [51]; Li et al. (2014) [52]							
USA	195	Randomized, controlled	24 weeks	2 60-min Tai Chi sessions per week ($n = 65$)	Resistance training ($n = 65$), stretching ($n = 65$)	Motor: Tai Chi did better than the resistance training and stretching group in maximum excursion and directional control ($p < 0.001$ for both). The Tai Chi group performed significantly better than stretching on all measures and outperformed the resistance training group on stride length and functional reach. Tai Chi lowered the incidence of falls as compared with stretching but not resistance training. Non-motor: significant improvement in PDQ-8 compared to resistance training, and both PDQ-8 and VPS compared to the stretching group	No serious adverse events
Cheon et al. (2013) [53]							
Korea	23	Randomized, controlled	8 weeks	3 60-min Sun-style Tai Chi sessions per week ($n = 9$)	Combined exercise ($n = 7$), non-exercise controls ($n = 7$)	Motor: non-significant trend toward improvement in UPDRS in both exercise groups; the combined exercise group performed better on measures of strength, flexibility of the upper limbs, and cardiovascular endurance, while the Tai Chi group performed better for measures of flexibility, strength of the lower limbs, agility, and cardiovascular endurance. Non-motor: tendency for improvement in quality of life scales in both exercise groups: emotional QOL in the Tai Chi group and social QOL in the exercise group	No serious adverse events
Zhang et al. (2015) [54]							

Table 2 (continued)

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
China	40	Randomized, controlled	12 weeks	2 60-min Yang-style Tai Chi sessions per week ($n = 20$)	Multimodal exercise training ($n = 20$)	Motor: no between-group difference in the BBS; improvement from baseline in both groups in mUPDRS, stride length, gait velocity, TUG test, though no between-group differences Qualitative: Tai Chi was harder to incorporate into a daily routine than exercise training.	No serious adverse events in either exercise group
Yang et al. (2017) [55]							
China	36	Randomized, controlled	13 weeks	3 60-min Yang-style Tai Chi sessions per week ($n = 19$)	Individual-based Yang-style Tai Chi ($n = 17$)	Motor: No statistically significant differences between groups Non-motor: Both groups had improvement from baseline in global non-motor symptoms and sleep; group-based had better cognition on MoCA ($p = 0.002$); no improvement in either group on HAMD Qualitative: Group-based had higher home exercise compliance rate (64.84% *vs* 51.17%, $p = 0.019$)	Did not report
Kurt et al. (2018) [56]							
Turkey	40	Randomized, controlled	5 weeks	5 60-min Ai Chi sessions per week ($n = 20$)	5 60-min land-based exercises per week ($n = 20$)	Motor: significantly improved dynamic balance ($p < 0.001$), BBS ($p < 0.001$), TUG test ($p = 0.002$), and mUPDRS ($p < 0.001$) in the Ai Chi group compared with controls. Both groups did improve relative to baseline in all measures. Non-motor: PDQ-39 was significantly improved from baseline in both groups. The Ai Chi group had significant improvement compared with the land-based exercise group	Did not report

6MWT = 6-min walk test; ABC = Activity-Specific Balance Confidence; AEs = adverse events; BBS = Berg Balance Scale; HAMD = Hamilton Depression Rating Scale; MoCA = Montreal Cognitive Assessment; mUPDRS = Unified Parkinson's Disease Rating Scale, motor subscale; PDQ-8 = 8-item Parkinson's Disease Questionnaire; PDQ-39 = 39-item Parkinson's Disease Questionnaire; QOL = quality of life; TUG = Timed Up and Go; UPDRS = Unified Parkinson's Disease Rating Scale; VPS = Vitality Plus Scale significant difference pre- and post-intervention on the mUPDRS, there were non-significant trends toward improvement in the Tai Chi group in dual-task gait stride-time variability, Activity-Specific Balance Confidence scale (ABC), Timed Up and Go (TUG) test, and PDQ-39.

Other studies have employed exercise comparator groups in an effort to determine if benefits can be attributed specifically to Tai Chi, rather than the effects of exercise in general. Cheon and colleagues [53] randomized patients to Tai Chi, a combined exercise control group or a non-exercise control group, and found that both exercise groups had significant improvement in upper limb strength and agility compared to non-exercise controls. While both groups had improved cardiovascular endurance compared to baseline, the combined exercise group was significantly greater than that of Tai Chi. Zhang and colleagues [54] randomized 20 patients to a Tai Chi intervention and 20 patients to a multimodal exercise group and found no difference between groups on the BBS, mUPDRS, stride length, gait velocity, and the TUG test; however, both groups had improved significantly from baseline. Another study by Kurt and colleagues [56] compared Ai Chi (an aquatic form of Tai Chi) to land-based exercise and found that both interventions led to improvement from baseline in dynamic balance, BBS, TUG test, mUPDRS, and PDQ-39, though this was significantly greater in the Ai Chi group.

The *New England Journal of Medicine* published the largest randomized, controlled trial of Tai Chi to date [51]. Li and colleagues [51] recruited 195 patients with PD and randomized participants to Tai Chi, resistance training, or stretching. When assessed specifically for measures of postural stability, which was the prespecified primary outcome measure, the Tai Chi group performed better than the resistance training and stretching groups in maximum excursion (assessment of the limits of self-excursion) and directional control (a measure of movement accuracy). The Tai Chi group also outperformed the stretching group in all secondary outcomes including the mUPDRS, the TUG test, and measures of gait (stride length and walking velocity) and strength. Importantly, the Tai Chi group also recorded fewer falls than either of the control groups, and this difference was sustained at 3 months. Quality of life was improved based on the 8-item Parkinson's Disease Questionnaire (PDQ-8) [52]. These results show that Tai Chi is at least as effective as other forms of exercise at improving the motor symptoms of PD, but more importantly, suggest that Tai Chi is a beneficial intervention to address postural instability and mitigate fall risk in this population. Indeed, many other studies have evaluated the effects of Tai Chi on balance and postural stability and demonstrated improvement on a variety of balance measures including the BBS [42, 43, 49, 56], the ABC scale [50], balancing on one foot [48], and the total number of falls [49].

Tai Chi for Non-motor Symptoms of Parkinson Disease

Hackney and Earhart [44] randomized a large group of 61 patients with PD to a variety of exercise interventions in their 2009 study, with the specific purpose of evaluating quality of life. In this study, only the tango group showed significant improvement from baseline on any of the PDQ-39 measures of quality of life, while participants in the Tai Chi, waltz/foxtrot, and control groups had no significant benefit. In a smaller study, Nocera and colleagues [46] randomized 21 people to Tai Chi or a non-contact control group, where participants were allowed to engage in voluntary, at-home physical activity without an instructor. They found that those in the Tai Chi group had significantly better scores on the PDQ-39 total score as well as the emotional well-being subscale. Yang and colleagues [55] explored whether non-motor symptoms might be more likely to improve in group-based Tai Chi rather than individual Tai Chi but found no significant difference between these interventions at 13 weeks. Both groups did have improvement from baseline in global non-motor symptoms (NMSs) and sleep, though neither showed improvement in depressive symptoms on the Hamilton Depression Rating Scale (HAM-D).

Conclusion

Tai Chi has proven to be a safe and feasible intervention for patients with PD. Participants report the intervention to be enjoyable and appropriate for their condition, and many would recommend to others and continue the intervention themselves after study completion [42, 57]. Measures of balance are consistently better after patients participate in structured Tai Chi programs, and it has also been shown to lessen fall risk. Importantly, the largest randomized, controlled trial of Tai Chi shows comparable effects on motor symptoms as a vigorous resistance training program, so it is reasonable to recommend Tai Chi as a component of a PD exercise routine. Few studies have specifically evaluated the effects of Tai Chi on non-motor symptoms, though some results suggest that it may positively impact quality of life. This warrants further investigation in dedicated clinical trials.

Qi Gong

Similar to Tai Chi, Qi Gong is a traditional Chinese practice that combines movement, posture, breathing, and meditation to enhance the flow of *qi*. Though less common in Western culture, Qi Gong has been practiced for nearly 5000 years in China and predates the study of Tai Chi. Though few studies have been conducted to evaluate its effect on PD, there seems to be a growing interest reflected by the recency of randomized clinical trials (Table 3).

Qi Gong for Motor Symptoms of Parkinson Disease

Six randomized, controlled trials have evaluated the effects of Qi Gong interventions on PD motor symptoms. Three studies compared Qi Gong to non-exercise controls and showed significant improvement in various motor outcomes: the proportion of patients with improved mUPDRS scores [59], baseline to 8-week changes in mUPDRS and total UPDRS [61], a decrease in muscle hardness using myometry [60], and improvement in the TUG test [60]. In a 7-week cross-over study comparing Qi Gong followed by aerobic exercise to aerobic exercise followed by Qi Gong, neither group had an improvement in motor function on the mUPDRS, though there was improvement on the 6-min walking test (6MWT) after aerobic exercise [62]. When compared to daily walking, Xiao and Zhuang [63] found significant improvements in the mUPDRS, motor symptoms at night (a PDSS subscale), 6MWT, TUG test, gait speed, and BBS in 45 patients with PD who completed 6 months of Qi Gong. The same group compared Baduanjin Qi Gong (a specific form of medical Qi Gong) to conventional physical therapy, and while the intervention group had significant improvement in the BBS, ABC, TUG test, and 6MWT relative to baseline, these results were not significant when compared to controls [64].

No studies have specifically addressed the effects of Qi Gong on balance as a primary endpoint, which is surprising given that it is a large focus of the practice. An open-label trial reported a decrease in double-support time after 6 weeks of Qi Gong, a measure of postural stability [58]. In the large study of 98 patients with PD described previously [64], participants had fewer falls and fractures after the intervention compared to their baseline assessment, and this approached significance when compared to the conventional physical therapy group.

Qi Gong for Non-motor Symptoms of Parkinson Disease

Many of these trials have also reported secondary non-motor outcomes, with mixed results that may reflect variability in comparator groups, frequency of treatment, and trial design. In the study by Schmitz-Hubsch and colleagues [59], there was a decrease in constipation, pain, and daytime sleepiness relative to controls after 8 weeks of twice weekly Qi Gong sessions. Turo (qi dance) improved the PDQL relative to non-exercising controls [61]. A study comparing Qi Gong to aerobic exercise, however, did not show significant improvement in the PDQ-39, nor did either group demonstrate improvement over the course of 7 weeks [62].

Sleep has been addressed most frequently in clinical trials. An open-label report of seven patients who completed 6 weeks of Qi Gong suggested improvement in some aspects of sleep quality by the end of the intervention [58]. In their large, randomized trial, Xiao and Zhuang [63] reported a secondary outcome that demonstrated improvement in the PDSS after participating in Qi Gong when compared to daily walking. Moon and colleagues [65] specifically addressed the effects of Qi Gong on sleep and TNF-α levels, an inflammatory cytokine involved in the sleep–wake cycle that has also been postulated to play a role in dopaminergic cell loss in PD [66, 67]. In this pilot trial, ten patients were randomized to Qi Gong or sham Qi Gong (featuring the traditional movements without breathing exercises or meditation) and reported a significant improvement in nighttime PD symptoms and the PDSS, which correlated to a decrease in TNF-α.

Conclusion

After participating in a focused Qi Gong intervention, patients tended to experience significant improvements in both motor and non-motor symptoms relative to their baseline performance. This effect is less consistent when comparing outcomes against controls, though this may be a result of the variability of control groups and the variety of outcome measures utilized in different trials. Additionally, similar to Tai Chi, Qi Gong seems to improve balance and reduce falls, though more data is needed to corroborate this claim. Multiple small studies have shown a modest improvement in various markers of sleep, and future studies should focus more on the effects of Qi Gong on other non-motor features of PD.

Yoga and Meditation

Yoga is an ancient Indian meditative and spiritual practice that has evolved in recent years to become a popular physical fitness and relaxation exercise. It involves a series of movements coordinated to breath and meditation, focusing on the mind–body connection. Based on these principles, yoga may improve motor symptoms of PD much like conventional exercise programs, but with an additional focus on non-motor outcomes as well. Randomized trials of yoga commonly incorporate meditation into the practice to evaluate the effects of these interventions on PD symptoms, though meditation has not been studied independently (Table 4).

Yoga for the Motor Symptoms in Patients with Parkinson Disease

Three randomized, controlled trials have compared regularly scheduled yoga or mindfulness sessions to non-exercising controls [71, 73, 74]. While all three reported an improvement in various measures of motor function and balance compared

Table 3 Reported clinical trials of Qi Gong for patients with Parkinson disease

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Wassom et al. (2015) [58]							
USA	7	Open-label	6 weeks	Weekly group "six-healing sounds" Qi Gong with twice daily at-home exercises	–	Motor: significant reduction in stride time (5.27%), gait velocity (8.73%), and double support time (9.01%); non-significant improvement in stride length (4.15%). Non-motor: improvement in some aspects of sleep quality (decreased motor symptoms at night, less disturbed sleep); there was no improvement in fatigue from baseline	Did not report
Schmitz-Hubsch et al. (2006) [59]							
Germany	56	Randomized, controlled	2 8-week sessions	Weekly 60-min Qi Gong sessions ($n = 32$)	Usual care ($n = 24$)	Motor: The proportion of patients with improvement in UPDRS was significantly greater at 3 months ($p = 0.008$), almost significant at 6 months ($p = 0.0503$), but not 12 months ($p = 0.635$) Non-motor: decreased constipation, decreased pain, reduced daytime sleepiness relative to controls; both groups reported decreased depression	Did not report
Liu et al. (2016) [60]							
Germany	56	Randomized, controlled	10 weeks	5 60-min Health Qi Gong sessions per week ($n = 28$)	Usual care ($n = 26$)	Motor: Muscle hardness of pronator teres using myometry was reduced compared to controls ($p < 0.01$); significant improvement in TUG test from baseline; improved hand–eye coordination and balance on various assessments	Did not report
Lee et al. (2018) [61]							
Korea	56	Randomized, controlled, wait-list, single-blind	8 weeks	Twice weekly 60-min Qi dance (Turo) sessions per week ($n = 25$)	Usual care ($n = 16$)	Motor: mUPDRS and total UPDRS were both significantly improved in the Turo group compared to controls ($p = 0.004$ and $p = 0.001$, respectively). There was a tendency toward improvement on the BBS ($p = 0.051$). Non-motor: PDQL improved compared to controls ($p = 0.049$), particularly social functioning and systemic symptoms	Did not report
Burini et al. (2006) [62]							
Italy	26	Randomized, controlled, cross-over	7 weeks of assigned treatment, followed by an 8-week "washout" without treatment, then 7 weeks of the other treatments	3 sessions of Qi Gong per week, followed by 3 sessions of aerobic exercise per week ($n = 13$)	3 sessions of aerobic exercise per week, followed by 3 sessions of Qi Gong per week ($n = 13$)	Motor: There was no change in mUPDRS in either group from baseline. The aerobic exercise group significantly improved their 6MWT and modified Borg scale (breathlessness) compared to baseline, but the Qi Gong group did not. Non-motor: no change in PDQ-39, BDI, Brown's disability scale in either group	Did not report

Table 3 (continued)

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Xiao and Zhuang (2016) [63]							
China	89	Randomized, controlled, single-blind	6 months	4 45-min sessions of Baduanjin Qi Gong (BDQ) per week plus 30 min of daily walking ($n = 45$)	30 min of daily walking only ($n = 44$)	Motor: The BDQ group had significant improvement in mUPDRS ($p = 0.038$), 6MWT ($p = 0.045$), TUG test ($p = 0.028$), gait speed ($p = 0.021$), and BBS ($p = 0.037$). Non-motor: The PDSS-2 total score was improved in the BDQ group (0.045) relative to controls, including the following subgroups: motor symptoms at night ($p = 0.037$) and disturbed sleep ($p = 0.045$)	Did not report
Xiao et al. (2016) [64]							
China	98	Randomized, controlled	6 months	4 60-min sessions of Baduanjin Qi Gong per week ($n = 49$)	4 sessions of conventional physical therapy per week ($n = 49$)	Motor: The Qi Gong group had significant improvement in TUG test, BBS, ABC, and 6MWT compared to baseline, but not when compared to controls. They also had fewer falls compared to baseline, which approached significance between groups	Did not report
Moon et al. (2017) [65]							
USA	10	Randomized, controlled	6 weeks	Twice daily at-home sessions of "six-healing sounds" Qi Gong plus a weekly group exercise class ($n = 5$)	Sham Qi Gong without breathing exercises or meditation plus a weekly group exercise class ($n = 5$)	Non-motor: significant reduction in TNF-α (an inflammatory marker) in the Qi Gong group, but not in controls. There were also significant improvements in the PDSS-2 total score ($p < 0.0005$) and PD symptoms at night subscale ($p < 0.05$), which correlated to a decrease in TNF-α	Did not report

6MWT = 6-min walk test; ABC = Activity-Specific Balance Confidence; AEs = adverse events; BBS = Berg Balance Scale; BDI = Beck Depression Inventory; BDQ = Baduanjin Qi Gong; mUPDRS = Unified Parkinson's Disease Rating Scale, motor subscale; PD = Parkinson Disease; PDQ-39 = 39-item Parkinson's Disease Questionnaire; PDQL = Parkinson's Disease Quality of Life Questionnaire; PDSS-2 = Parkinson's Disease Sleep Scale 2; TNF-α = tumor necrosis factor-α

Table 4 Reported clinical trials of yoga for patients with Parkinson disease

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Hall et al. (2011) [68]							
UK	1	Case report	8 weeks	Weekly 60-min yoga session	–	Motor: The participant had a non-significant improvement on BBS and TUG test. There was no consistent trend in hip and ankle range of motion. Non-motor: no change from baseline in the PDQ-39	Did not report
Moriello et al. (2013) [69]							
USA	1	Case report	6 months	Twice weekly 90-min yoga session plus a home exercise program for 12 weeks, followed by a personalized home exercise program incorporating yoga	–	Motor: The participant had an improvement from baseline to 6 months on the HiMAT (+ 11 points). Non-motor: PDQ-39 score improved after 6 months (− 16 points)	Did not report
Boulgarides et al. (2014) [70]							
USA	10	Open-label	8 weeks	Weekly 60-min yoga session	–	Motor: no change in mUPDRS, BBS, mDGI, and FRT after the intervention; near-significant improvement in lower extremity strength and flexibility, single limb balance, and 30-s chair stand after the intervention Non-motor: near-significant improvement on HADS after the intervention Qualitative: 5/10 continued to participate in paid yoga classes	No adverse events
Colgrove and Sharma (2012) [71]; Sharma et al. (2015) [72]							
USA	13	Randomized, controlled	12 weeks	Twice weekly 60-min Iyengar Hatha yoga sessions ($n = 8$)	Usual care ($n = 5$)	Motor: significant improvement in mUPDRS compared to baseline ($p = 0.006$), though there was no difference between groups; the yoga group also had improvement in diastolic BP ($p = 0.036$) and average forced vital capacity ($p = 0.03$). Non-motor: trend toward significance on the GDS after intervention Qualitative: Yoga participants reported more positive symptom changes including tremor reduction, more relaxation, and less fatigue; 2 patients reduced medications	No adverse events
Cheung et al. (2018) [73]							
Australia	20	Randomized, wait-list-controlled	12 weeks	Twice weekly 60-min group-based Hatha yoga ($n = 10$)	Usual care ($n = 10$)	Motor: The mUPDRS was improved compared to controls after the intervention. Non-motor: no change in sleep quality, depression, cognitive function, and global quality of life; the yoga group had worse scores on the sleep and outlook subscales on PDQUALIF. Qualitative: Most (17/20) stated they "definitely enjoyed" the program	No adverse events
Van Puymbroeck et al. (2018) [74]; Walter et al. (2019) [75]							
USA	27	Randomized, wait-list-controlled	8 weeks	Twice weekly 60-min Hatha yoga sessions ($n = 15$)	Usual care ($n = 12$)	Motor: greater functional gait in the yoga group compared to controls; improvement in mUPDRS and freezing of gait compared to baseline; within the yoga group, significant improvement from baseline in postural stability (mini-BESTest), fall risk, Activity-Specific Balance Confidence Scale, Falls Management Scale Non-motor: Within the yoga group, there was a significant improvement in PFS-16 and PDQ-8 from baseline	Did not report

Table 4 (continued)

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Bega and Stein (2016) [76]							
USA	17	Randomized, single-blind, controlled	12 weeks	Twice weekly 60-min Iyengar yoga ($n = 9$)	Resistance training ($n = 8$)	Motor: Both groups had improvement from baseline on the mUPDRS, TUG test, and BBS, but no significant between-group differences. Non-motor: Both groups had improvement from baseline on PDQ-39, but no significant between-group difference. Qualitative: The program was feasible, as 13/17 went to at least 75% of classes, though this was significantly higher than the resistance training group. In the yoga group, 8/9 agree that class was enjoyable and beneficial	No adverse events
Ni et al. (2016a) [77]; Ni et al. (2016b) [78]							
USA	41	Randomized, controlled	12 weeks	Twice weekly 60-min group power yoga sessions ($n = 15$)	Twice weekly power training ($n = 14$), non-exercise controls participating in a 1-h per month health education course ($n = 12$)	Motor: Both exercise groups scored significantly better on mUPDRS, BBS, mini-BESTest, TUG test, functional reach (less affected side), 10-m walking, muscle strength and power (1 repetition maximum), and peak power compared to controls, but there were no between-group differences. In a secondary analysis evaluating yoga *versus* non-exercise controls, the yoga group had significant improvement from baseline in bradykinesia, rigidity, muscle strength, and power. Non-motor: There was significant improvement on the PDQ-39 sum compared to controls, and in the subdomains of mobility and ADLs.	
Kwok et al. (2019) [79]							
China	138	Randomized, single-blind, controlled	8 weeks	Weekly 90-min Hatha yoga sessions ($n = 71$)	Weekly 60-min stretching and resistance training exercise ($n = 67$)	Motor: Both groups had improvement in mUPDRS and TUG test compared to baseline, but there were no between-group differences. Non-motor: There was a significant improvement in HADS compared to controls	

ADLs = activities of daily living; AEs = adverse event; BBS = Berg Balance Scale; BP = blood pressure; FRT = Functional Reach Test; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HiMAT = High-level Mobility Assessment Tool; mDGI = modified Dynamic Gait Index; Mini-BESTest = Mini Balance Evaluation Systems Test; mUPDRS = Unified Parkinson's Disease Rating Scale, motor subscale; PDQ-8 = 8-item Parkinson's Disease Questionnaire; PDQ-39 = 39-item Parkinson's Disease Questionnaire; PDQUALIF = Parkinson's Disease Quality of Life Scale; PFS-16 = Parkinson's Disease Fatigue Scale; TUG = Timed Up and Go to baseline, only one [73] showed significant improvement relative to non-exercising controls.

Three additional studies have compared yoga interventions to active exercise control groups to determine if there may be benefits specific to this physical practice. One such study compared yoga to power training and non-exercise controls and found that both the yoga and power training groups had significantly better scores on measures of motor function, balance, gait, and muscle strength compared to controls, but not to each other [77]. When compared specifically with the non-exercise controls in a separate analysis, the yoga group did have reduced bradykinesia and rigidity, with increased muscle strength and power [78]. Two separate studies, one of 17 patients evaluated after 12 weeks [76] and a more recent 8-week study involving 138 patients [79], compared yoga to resistance training and found improvements in measures of motor function and balance (mUPDRS, TUG test, BBS) in all exercise groups post-intervention, though this was again not different between groups.

Yoga for Non-motor Symptoms in Patients with Parkinson Disease

Kwok and colleagues' [79] large study comparing yoga to resistance training was designed to evaluate the effects of this intervention on anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). In addition to the motor benefits noted above, they noted a significant interaction effect on the HADS (both anxiety and depression scores), certain subscales on the Holistic Well-being Scale (HWS), and PDQ-8 that favored the yoga intervention [79]. A secondary analysis of one study noted previously found an improvement in fatigue on the 16-item Parkinson's Disease Fatigue Scale (PFS-16) and quality of life on the PDQ-8 compared to baseline, but not controls [75]. In their study, Bega and Stein [76] showed significant improvement in anxiety and emotional dysregulation on the Quality of Life in Neurological Disorders (Neuro-QoL) scale compared to resistance training.

Results are otherwise mixed as to the benefits of yoga on non-motor symptoms; however, many of these studies are not specifically powered to detect change on these outcomes.

The Effects of Yoga on Imaging and Biomarkers

Data is limited regarding the effects of yoga interventions on radiographic and chemical changes in the body. Pickut and colleagues [80] conducted a randomized, controlled trial to evaluate the effects of a mindfulness-based intervention on brain structure using magnetic resonance imaging (MRI). In prespecified regions of interest, there was increased gray matter density in the right amygdala and bilateral hippocampi in patients who had undergone 8 weeks of mindfulness when compared with non-exercise controls. Whole-brain analysis revealed a large cluster of activity in the right caudate and a smaller cluster in the left caudate, areas that are involved in the pathophysiology underlying PD. In the randomized trial by Cheung and colleagues [73], one outcome measure evaluated changes in markers of oxidative stress, though these were not different between the intervention and control groups.

Conclusion

These studies suggest that yoga is likely as effective as other exercise routines to exert some improvement on the motor symptoms of PD, but not necessarily better at improving non-motor symptoms. More studies are necessary to explore the effects of yoga, specifically the meditation component, on the non-motor aspects of PD, as one might expect to find more substantive changes on mood, behavior, and sleep similar to what is seen in the general population [81, 82]. Interestingly, there is very little data in the literature about the effects of meditation separate from what is incorporated into yoga sessions, and this is another area for future study. Regardless, qualitative analysis of yoga programs suggests that patients find them to be feasible, enjoyable, and beneficial for their symptoms [70, 72, 73, 76], and it is reasonable to recommend this therapy as a component of a PD exercise routine.

Cannabis

Cannabis has received growing attention over the past decade due in part to changing legislation in the USA and across the globe, as well as reports of benefit in a variety of conditions. *Cannabis sativa* is plant of the Cannabaceae family, with more than eighty biologically active chemicals according to the U.S. Food and Drug Administration [83]. The most well known of these compounds include cannabidiol (CBD) and delta-9-tetracannabinol (THC). The suspected mechanism of action of these compounds involves interaction with endocannabinoid receptors CBR1 and CBR2, both G protein-coupled receptors, of which the former is highly expressed in the central nervous system (particularly the olfactory bulb, hippocampus, thalamus, and basal ganglia) and the latter expressed more peripherally [84, 85]. While there is consistent evidence that THC binds actively to CBR1, there is still controversy over how CBD interacts with endocannabinoid receptors and if this leads to neuroprotection [85, 86]. While there is great interest in this link, clinical trials are lacking in PD and other neurological conditions (Table 5). To date, only Epidiolex, which is a purified form of CBD, has been FDA-approved for the treatment of seizures associated with Lennox–Gastaut syndrome or Dravet syndrome [83].

In a Web-based survey through the Michael J. Fox Foundation completed by 454 patients with PD, two thirds had tried cannabis at any point and one third continued to

Table 5 Reported clinical trials of cannabis for patients with Parkinson disease

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Frankel et al. (1990) [87]							
UK	5	Case series	1 session	Smoking 1 g marijuana	–	Motor: no improvement in tremor after the intervention	Drowsiness
Chagas et al. (2014b) [88]							
Brazil	4	Case series	Variable	CBD capsules up to 300 mg/day	–	Motor: prompt and substantial reduction in RBD-related events	Did not report
Zuardi et al. (2009) [89]							
Brazil	6	Open-label	4 weeks	CBD capsules up to 400 mg/day	–	Motor: improvement in total UPDRS score from baseline Non-motor: The BPRS, PPQ, and CGI all improved from baseline	No adverse effects and no change in cognition on MMSE or FAB
Lotan et al. 2014 [90]							
Brazil	22	Open-label	1 session	Smoking cannabis (variable dosing)	–	Motor: The mUPDRS improved 30 min after smoking cannabis, including tremor, rigidity, and bradykinesia. Non-motor: Visual Analog Scale, present pain intensity scale both improved from baseline Qualitative: 12 reported greatly improved sleep quality, and 8 had mild relief	Dizziness in 1 patient; long-term effects include somnolence, drowsiness, palpitations, and bad taste from smoking
Shohet et al. (2017) [91]							
Israel	20	Open-label	1 session	Smoking or vaporizing cannabis	–	Motor: The mUPDRS significantly improved 30 min after smoking. Non-motor: There was a significant improvement in the VAS from baseline, and a trend toward improvement in PRI. After long-term exposure, the mean heat pain threshold in the affected limb decreased significantly	Did not report
Leehey et al. (2020) [92]							
USA	13	Open-label	10–15 days	CBD (Epidiolex) up to 25 mg/kg/day	–	Motor: Total and mUPDRS scores improved from baseline (17.8% ($p = 0.012$) and 24.7% ($p = 0.004$), respectively)	Mild adverse events in all patients, including diarrhea (85%), somnolence (69%), fatigue (62%), weight gain (31%), dizziness (23%), abdominal pain (23%), and headache, weight loss, nausea, anorexia, and increased appetite (all 5%). 5 had increased LFTs
Sieradzan et al. (2001) [93]							
USA	7	Randomized, double-blind, placebo-controlled	2 sessions, 2 weeks apart	Cannabinoid receptor agonist, nabilone	Placebo	Motor: significant improvement in levodopa-induced dyskinesias, with no change in "off" or "on" time	Vertigo, postural hypotension, mild sedation, dizziness, hyperacusis, "floating sensation," partial disorientation, formed visual hallucinations
Carroll et al. (2004) [94]							
UK	19	Randomized, double-blind, placebo-controlled, cross-over study	4 weeks	Cannador capsules—2.5 mg THC, 1.25 cannabidiol per capsule with dose titration	Placebo	Motor: no improvement in dyskinesia, the primary endpoint Non-motor: no improvement in PDQ-39, sleep, and pain	No serious adverse events Physical and psychological adverse events were similar in both groups, but more than double in the cannabis group

Table 5 (continued)

Study	Size	Design	Duration	Intervention	Controls	Outcomes	AEs
Chagas et al. (2014a) [95]							
Brazil	21	Randomized, double-blind, placebo-controlled	6 weeks	CBD capsules 75 mg/day ($n = 7$), CBD capsules 300 mg/day ($n = 7$)	Placebo	Motor: no improvement in any part of UPDRS compared to placebo ($p > 0.05$) Non-motor: Total PDQ-39 improved at 300 mg/day compared to placebo ($p = 0.05$)	No adverse events

AEs = adverse events; BPRS = Brief Psychiatric Rating Scale; CBD = cannabidiol; CGI = Clinical Global Impression; LFTs = liver function tests; mUPDRS = Unified Parkinson's Disease Rating Scale, motor subscale; PDQ-39 = 39-item Parkinson's Disease Questionnaire; PPQ = Parkinson Psychosis Questionnaire; PRI = Pain Rating Index; RBD = Rapid Eye Movement Sleep Behavior Disorder; THC = tetrahydrocannabinol; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = Visual Analog Scale

use cannabis to treat various symptoms of PD [96]. On these self-report scales, patients note improvement in memory, mood, and fatigue. Cannabis use is common outside of the USA as well. In an anonymous survey study of 339 patients with PD in the Czech Republic, a quarter of respondents had tried cannabis at some point and nearly half reported some benefit to a variety of motor symptoms, including the cardinal features of PD and dyskinesia [97]. In a smaller interview study of 47 patients in Israel, most reported improvement after cannabis use, including reduction in falls, stiffness, and tremor, as well as non-motor symptoms including pain, mood, and sleep quality [98]. Despite these benefits, however, more than half reported adverse events that included confusion, anxiety, hallucinations, amnesia, psychosis, dizziness, and unsteadiness, and inhalation side effects of cough and dyspnea. In a 2015 survey conducted in Colorado shortly after the legalization of recreational cannabis use (enacted in 2012 and implemented in 2014), only 4.3% of patients reported using it for PD symptoms though the majority (78%) found it to be useful [7].

Cannabis for Motor Features of Parkinson Disease

In an open-label, observational study of 22 patients with PD, mUPDRS scores were significantly improved 30 min after smoking 0.5 g of cannabis [90]. Another group, conversely, noted no improvement in tremor in five patients with PD shortly after smoking 1 g of marijuana [87]. In a randomized, placebo-controlled trial, a Brazilian group studied two dosages of CBD—75 mg/day and 300 mg/day—in capsule form over 6 weeks, and also did not find a significant difference on UDPRS scores, plasma brain-derived neurotrophic factor (BDNF) levels, or proton magnetic resonance spectroscopy scans compared to placebo, though there was a significant improvement in quality of life reported in the higher dose on the PDQ-39 [95].

Researchers from the UK reported a randomized, double-blind study of Cannador (an oral capsular formulation with a 2:1 THC:CBD ratio) using a cross-over design, aimed specifically at measuring improvements in levodopa-induced dyskinesias. Nineteen patients were randomized to receive either placebo followed by cannabis or vice versa; there were no reported improvements in measures of dyskinesia or subjective reports, though the drug was well tolerated [94]. This is incongruent with previous data, where a smaller placebo-controlled trial of seven patients with PD demonstrated that the cannabinoid receptor agonist nabilone could decrease levodopa-induced dyskinesias compared to placebo [93]. These studies provide mixed results as to the potential benefits of cannabis on dyskinesias and suggest further studies are warranted.

Cannabis for Non-motor Features of Parkinson Disease

In 2009, Zuardi and colleagues [89] reported the results of an open-label study of CBD for patients with PD and psychosis, starting with 150 mg/day and titrating up to 400 mg/day. Their results show a significant improvement from baseline to 4 weeks on all subscales of the Brief Psychiatric Rating Scale (BPRS), Parkinson Psychosis Questionnaire (PPQ), UPDRS total score, and Clinical Global Impression-Improvement (CGI-I) scale, without worsening of the Mini-Mental State Examination (MMSE) or Frontal Assessment Battery (FAB). The same group later described four patients with PD and rapid eye movement sleep behavior disorder (RBD) who were treated with CBD up to 300 mg per day for 6 weeks, and found that they had "prompt and substantial" reduction in the frequency of RBD-related events without appreciable side effects [88]. No other studies have included measures of RBD to corroborate this finding. Importantly, these compounds did not include THC, which is more likely to cause psychotropic side effects as noted below.

Shohet and colleagues [91] reported an open-labeled trial of 20 patients with PD reporting significant pain at baseline and found that the cannabis improved the UDPRS scale, Pain Rating Index (PRI), and Visual Analog Scale (VAS) of the McGill Pain Questionnaire. Furthermore, they evaluated temperature thresholds after short- and long-term exposures and found that the mean cold pain threshold decreased significantly in the more affected limb after short-term exposure, and the mean heat pain threshold decreased significantly after long-term exposure. They deduced that cannabis may improve motor function and lessen pain perception in patients with PD.

Safety and Tolerability of Cannabis

More than any other intervention reported in this review, safety concerns make the use of cannabis controversial, though certain adverse effects are dependent upon the method of ingestion. Open-label studies of inhaled marijuana cite common side effects of dizziness and drowsiness, plus smoking-related complications of cough or a foul taste in the mouth [87, 90]. The study by Carroll and colleagues [94] used a THC-containing product and reported more than double the adverse effects in the experimental group, including physical (dry mouth, altered taste, gastrointestinal symptoms, and dizziness) as well as psychological (drowsiness, detached sensation, paranoia, poor concentration and memory, and vivid dreams) effects.

Pure cannabidiol, however, is non-psychotropic and generally well tolerated up to doses of 1500 mg/day [99, 100]. Open-label studies report few side effects, though only one trial to date has specifically evaluated safety and tolerability. This recently published, open-label study of cannabidiol by Leehey and colleagues [92] reported various adverse effects in all 13 patients included in the trial. Symptoms were generally mild, but included diarrhea (85%), somnolence (69%), fatigue (62%), weight gain (31%), dizziness (23%), abdominal pain (23%), and headache, weight loss, nausea, anorexia, and increased appetite (each 5%).

Conclusion

Though many patients with PD report use of cannabis at some point during their disease course, large, randomized, placebo-controlled trials are lacking. The available data shows mixed results, likely due in part to the heterogeneous administration methods employed in various studies and the lack of standardized products. Cannabis also has a greater side effect profile than other interventions mentioned in this review, though some side effects can be mitigated by ingesting, rather than inhaling, the drug. Regardless, patients should be made aware of the potential adverse effects of cannabis products, especially in light of the growing ease with which patient can obtain it.

Conclusions

There is a growing interest in the use of complementary therapies along with traditional dopaminergic therapy to alleviate the motor and non-motor symptoms of PD. Over the past 20 years, a vast number of studies have been published that evaluate the benefits of complementary therapies, with variable results. Of the interventions reviewed here, the most consistent positive finding is the improvement in gait and balance that results from participation in Tai Chi or Qi Gong. In general, the physical interventions (Tai Chi, Qi Gong, yoga) reviewed here seem to be as effective as other exercise regimens at improving motor symptoms of PD, but generally do not outperform them. Non-motor symptoms are often secondary outcomes and may not reach significance compared to controls due to lack of power. Patient-reported quality of life tends to improve from baseline in the experimental group of many of these interventions, but this change is often not significantly different from that seen in controls.

Fortunately, many of the treatments mentioned in this review are safe and well tolerated. No major adverse events were reported in any study, though it is important to consider that participants tend to have greater oversight when exercising as part of a clinical trial than they do when exercising independently, so the risk of injury may in fact be greater. Survey data routinely shows these interventions to be enjoyable and appropriate for patients with PD, and despite the lack of objective improvement, patients subjectively cite positive benefit to motor and non-motor symptoms. Cannabis is generally the exception, as it can have psychotropic and physical side effects that are dependent upon the dosage, formulation, and route of ingestion.

Trial design is a major factor that contributes to the variability seen in these results. Studies of an active intervention are prone to inadequate blinding of the intervention by participants, as patients are aware of whether or not they are participating in the experimental group. This certainly contributes to the improvement that is often seen from baseline in open-label and non-exercise control studies, particularly on patient self-report measures. Some of this effect can be mitigated by blinding evaluators. Additionally, these studies have variable and sometimes inadequate control groups. When compared to baseline markers, patients participating in complementary treatments often demonstrate improvement from baseline after the intervention, but the lack of comparative benefit relative to controls suggests a high likelihood of placebo effect from participating in clinical trials. This phenomenon is well established in PD [101], as the anticipation of receiving an intervention likely leads to some degree of improvement in these patients, which is best observed in the sham-controlled acupuncture trials [27]. In this review, it is difficult to directly compare individual trials due to the heterogenous implementation of the interventions. For example, exercise classes are highly variable due to differences in the instructors, acupuncture is often an individualized procedure that is based on the patients' needs, and cannabis can be used in various formulations, just to name a few.

Similar to previous reviews of complementary therapies for PD, we do not suggest that these complementary therapies should supplant traditional, evidence-based therapies. However, the current literature does suggest a role for complementary therapies as a component of a multifaceted approach to disease management and reinforce the idea that exercise of any kind can provide short-term benefits on various motor and non-motor symptoms. Larger studies with appropriate control groups and adequate blinding can certainly help to provide more insight into this ongoing debate.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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